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Quantitative Assessment of Brain Networks in Children with Sturge-Weber Syndrome Using Resting State Functional MRI

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Abstract

In this study, we examined whether topologic network analysis, using resting state functional Magnetic Resonance Imaging (MRI), can detect abnormalities of functional brain connectivity in children with unilateral brain injury due to Sturge-Weber syndrome. Three children with Sturge-Weber syndrome (age: 1, 3, 10 years) underwent structural and resting state functional MRI, glucose metabolism Positron Emission Tomography (PET), and neurocognitive evaluation. Eight different resting state networks were compared between the affected and unaffected hemispheres by quantitatively accessing communication efficiency measures. Significantly reduced efficiency values were found in all three patients. Visual network deficiency was present in both children with a visual field defect; frontal network abnormalities were associated with fine motor impairment. Location of network abnormalities corresponded to and, in some cases, extended beyond structural MRI and glucose PET abnormalities. The presented approach can detect early functional abnormalities of specific brain networks in children with Sturge-Weber syndrome.

Keywords

Sturge-Weber syndrome; resting state functional network; topologic network analysis; neurocognitive functions

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Author Contributions

JWJ and CJ were both responsible for the organization and execution of the research project; design, review, software implementation, and interpretation of statistical analysis. HC was responsible for patient recruitment, contributed to creating study concept, reviewed and critiqued the manuscript. MB and WG were responsible for behavioral assessment. JWJ wrote the first draft of the manuscript. CJ, HC, and MB revised the manuscript. All authors gave final approval of the version to be published.

Declaration of Conflicting Interests

The authors declared no potential of interest with respect to the research, authorship and/or publication of this article.

Ethical Approval

The Human Investigations Committee of Wayne State University granted permission for acquiring MRI and PET scans from all participants. Informed consent forms were signed by the parents of all participants to approve the use of patient information or material for scientific purposes.

Introduction

Sturge-Weber Syndrome is a neurocutaneous disorder associated with malformation of the leptomeningeal vascular beds (traditionally called angioma) due to a failure of the primitive cephalic venous plexus to regress and properly mature *in utero*¹. Neurological manifestations, including fine motor deficit, visual field cuts, progressive cognitive decline and seizures, most often start during the first year of life and show a highly variable clinical course in affected children². Since cerebral abnormalities affect only one hemisphere in 85% of the cases, Sturge-Weber syndrome is also a unique clinical model to study neurocognitive effects of an early, progressive, unilateral brain damage for which there is no specific treatment to alter the often-progressive clinical course^{3–5}.

Advanced neuroimaging techniques have improved the detection of vascular and brain tissue abnormalities in Sturge-Weber syndrome, identified imaging markers associated with specific neurocognitive complications, and discovered mechanisms of brain damage and reorganization^{4–10}. Our recent studies have also suggested that both grey matter and white matter injury may contribute to Sturge-Weber syndrome related neurocognitive deficits^{4,6,9,10}. Early onset white matter damage may lead to disruptions in brain connectivity thus leading to abnormalities that impact the development of intrinsic resting-state brain networks^{11,12} (such as default mode, visual, sensory-motor, and language networks), which are present in the human brain both during task performance and rest, across degrees of consciousness.

Recently, resting state functional Magnetic Resonance Imaging (fMRI) has facilitated the non-invasive mapping of large-scale neural network dysfunction¹³. Resting state functional MRI is a task-free functional MRI acquisition where we measure “resting state” fluctuations (0.01–0.08 Hz) in blood oxygen level-dependent signals related to spontaneous neural activity across brain regions. Correlation analysis of these spontaneous fluctuations has proven effective for assessing functional network alterations in various neurological and psychological disorders^{14–16}.

In the present study we applied quantitative resting state functional MRI-based network analysis to assess pathophysiological changes in intrinsic functional brain networks of children with unilateral Sturge-Weber syndrome. We asked whether the functioning of specific intrinsic networks might be altered in the affected hemisphere. If so, we assessed whether such altered networks would be concordant with brain structural and metabolic abnormalities, as identified by other imaging methods, and whether network alterations might correlate with specific neurocognitive dysfunctions.

Methods

Subjects

The study included three children with unilateral Sturge-Weber syndrome (a 10-year old boy, a 3-year old girl, and a 1-year old girl). All three had unilateral leptomeningeal enhancement in posterior brain regions on contrast-enhanced MRI. The two older children had a history of focal seizures but had not had a clinical seizure for at least 7 months. The

oldest boy also had a history of stroke-like episodes. The youngest child had a history of infantile spasms and was seizure-free for several months. All three children took antiepileptic drugs (levetiracetam and/or oxcarbazepine) at the time of the evaluation. All three children underwent a neurological examination on the day of the MRI scans, and all three children underwent detailed neuro-psychological or (one year old) developmental and behavioral assessments, as described previously^{9,10}.

Data Acquisition

MRI acquisition—A Siemens MAGNETOM Trio 3T scanner (Siemens Medical Solutions, Erlangen) with a 12-channel head array coil was used for all resting state functional MRI studies using T2*-weighted echo-planar imaging sequence at repetition time = 2000 ms, echo time = 35 ms, flip angle = 90 degrees, field of view = 240 mm, matrix size = 64×64, slice thickness = 4 mm, and zero gap covering the whole brain. Resting state functional MRI studies were done before contrast injection, before (3-year old), without (10-year old, where two five-minute session data were acquired before contrast injection to study test-retest reproducibility) or after sedation (1-year old). The 10-year old child was not sedated at all. Sedation was performed with pentobarbital (3 mg/kg) followed by fentanyl (1µg/kg) (for the 3-year old, induced after resting state functional MRI acquisition) or pentobarbital (3 mg/kg) followed by a booster dose of pentobarbital (1.5 mg/kg, 1-year old child, induced before any MRI acquisition). Additional MR sequences, including pre-and post-contrast T1-weighted, pre-contrast fluid attenuated inversion recovery, T2, susceptibility weighted sequences and MR venography were acquired, as described previously^{8–10}.

Positron Emission Tomography (PET) scanning—All three patients underwent PET scanning of brain glucose metabolism using 2-deoxy-2-[¹⁸F]fluoro-D-glucose, under a research protocol, 1 day after the MRI scan, as described previously⁹. Electroencephalography was monitored during the uptake period and showed no evidence of seizures or interictal spiking. No sedation was applied during the uptake period. Areas of abnormal glucose metabolism were evaluated visually by two of the investigators (HTC and CJ).

Data analysis of resting state functional MRI

The preprocessing steps using Statistical Parametric Mapping 8 (www.fil.ion.ac.uk/spm) included: first, correction of systematic, slice-dependent time shifts; second, rigid body correction for inter-frame head motion within and across all scans; third, spatial normalization to standard head space for group comparison; fourth, spatial smoothing with an isotropic Gaussian kernel of 8 mm full width half maximum to increase statistical power.

The resulting images were detrended to abandon linear trend, temporally filtered with a Chebyshev band-pass filter (0.01 Hz - 0.08 Hz), and regressed out with the following covariates: rigid body realignment parameters, average white matter signal, average ventricular system signal, and global signal¹⁷. Filtered-regressed time series were finally parcellated into 116 network node regions by using the Automated Anatomical Labeling

atlas¹⁸ (www.ansir.wfubme.edu). The average time series of individual node was used to represent spontaneous neural activity in subsequent network analysis.

According to anatomical labels of individual nodes, we constructed a total of eight brain networks including frontal lobe, temporal lobe, parietal lobe, occipital lobe, default mode, motor, language, and visual networks (Fig. 1). To measure topological efficiency at individual networks, a weighted undirected network matrix was produced by taking a proportional threshold to the cross-correlation coefficient matrix of node time series (i.e., 0 proportional threshold = 1). Two effective network measures were then evaluated at every discrete value of proportional threshold¹⁹: global communication efficiency and local communication efficiency. Global communication efficiency measures the degree of functional *integration* to quantify the capacity of parallel information process, where a low value of global communication efficiency indicates the presence of disconnected nodes inhibiting parallel processes. In contrast, local communication efficiency is a measure of functional *segregation*, where a low value of local communication efficiency quantifies the reduction of densely interconnected nodes known as functional clusters or modules.

We evaluated the summation of efficiency value over the full threshold range of proportional threshold and used the resulting scalar as an imaging marker to quantify the functional efficiency in individual networks. The hemispheric (right/left) ratio was finally utilized to assess the degree of hemispheric network impairment in the affected hemisphere.

Results

Resting state functional MRI detected altered functional networks in all three patients with Sturge-Weber syndrome where resting state functional MRI analysis quantified disrupted connectivity in affected brain regions (Fig.2). Reduced hemispheric global communication efficiency, indicating corrupted functional integration, was found in the affected hemisphere in regions abnormal on both PET and MRI. Furthermore, this alteration was clearly noticeable in affected networks of all three patients, corresponding to the location of the lesions demonstrated on structural MRI and PET (Fig.2, Table 1). We also found significantly reduced local communication efficiency in the affected hemisphere of all three patients, in a pattern that was similar to global communication efficiency (no detailed data shown).

In individual cases, slightly reduced global communication efficiency was observed in the right temporal and visual networks of the 10-year old child with a right superior parietal, occipital, temporal lesion. Interestingly, the parietal network showed no obvious abnormality but the right frontal network showed reduced global communication efficiency. Consistent with this finding, this child had impaired fine motor function in the left hand but no gross hemiparesis. He also had visual field deficit in the upper quadrant and borderline processing speed. He performed in the average-low average range on all other cognitive measures.

The 3-year old child with severe right parieto-temporo-occipital and milder frontal involvement showed markedly reduced α_G in most networks except language and motor networks (Table 1). She had a left visual field deficit, and mild weakness in her left hand but

not her arm. She had reduced fine motor dexterity bilaterally, left worse than right. She had relatively decreased performance intelligence quotient (76) as compared to verbal intelligence quotient (110).

In the 1-year old child with a relatively small left medial occipital abnormality, an apparent decrease in global communication efficiency was confined to the left occipital network, while the visual network was symmetric. She had no neurological symptoms and her development was measured to be age-appropriate.

In addition, hemispheric ratio of global communication efficiency was decreased in each functional network of Sturge-Weber syndrome, again corresponding to cortical lesions (Fig. 3). Compared with age and gender-matched normal controls, showing negligible hemispheric lateralization, it is clear that the patients with Sturge-Weber syndrome were characterized by significantly lateralized values of global communication efficiency in hemispheric, default mode, and visual network in the affected hemisphere.

To investigate test-retest reproducibility of the network parameters, two different network parameters, global communication efficiency and local communication efficiency, were compared between two, repeated resting state functional MRI data, in the 10-year old child (Fig. 4). Nearly perfect correlation (0.99–1.00) was found in the magnitude of global and local communication efficiency across the two datasets, indicating high reproducibility.

Discussion

Multiple brain regions are functionally linked to each other during rest, forming resting state networks. This study demonstrates that altered functional efficiency measures of resting state networks can be an effective marker to quantify injured brain tissues and related neurocognitive deficits in children with Sturge-Weber syndrome. Resting state functional network abnormalities can extend beyond structural and metabolic abnormalities identified by other imaging modalities. Importantly, the applied resting state functional MRI approach, utilizing global and local efficiency measures, may be useful for exploring and monitoring early brain functional abnormalities in young children with Sturge-Weber syndrome and also children with brain injury from other causes.

Since task-based functional MRI techniques are not practical in infants and young children because of poor co-operation, there are limited studies in this population. By comparison, resting state functional MRI techniques have been utilized successfully to investigate early development of the resting state network at various levels of arousal^{20–22}. Most resting state networks have been identified in children during different levels of sleep, under sedation, and in coma, indicating that intrinsic network correlations are not suspended by these conditions²². However, the effects of level of arousal on connectivity strength remain incompletely understood, with correlation strength modulated in a network-specific manner by state^{23–24}. To avoid this ambiguity, the present study utilized a proportional threshold that enables us to construct a weighted undirected network matrix without depending on the absolute value of correlation coefficients. Importantly, our preliminary results suggest that this thresholding technique renders the network parameters unchanged in repeated testing

and provide meaningful data both in awake and sedated states across a wide age-range. Thus, the presented approach might be well suited for longitudinal studies to assess early brain development in neonates and infants.

Albeit preliminary due to the small sample size and lack of detailed statistical comparisons, the present study strongly suggests that reduced network values can be reliably measured in young children and are related to injury of affected brain regions. Importantly, network abnormalities can extend beyond the structural lesions or even metabolic abnormalities seen on structural MRI and PET, respectively. On the other hand, networks may function well in some areas that appear abnormal on other imaging. This suggests that resting state functional MRI provides complementary information to other imaging modalities. Importantly, network abnormalities appear to correlate with specific neurocognitive dysfunctions. For example, we have detected visual network deficiency in both children with a visual field defect; frontal network abnormalities associated with motor impairment, and lack of language network abnormalities in children with normal verbal intelligence quotient. Interestingly, no obvious motor network abnormalities were found in any of the children, probably because none of them had major motor involvement. Impairment in fine motor functions appears to be better reflected in abnormalities identified in the frontal network. Thus, these resting state functional MRI abnormalities may provide objective, functional information on specific neurocognitive domains, and may be predictive of dysfunction in young children at the early disease stage, when objective clinical evaluation of specific neurocognitive abnormalities is difficult. This could be further addressed in prospective, longitudinal studies.

Resting state networks are interconnected by anatomical white matter tracts¹². It is likely that the reduced network efficiency, observed in our patients, results from impaired axonal connections among interconnected brain regions belonging to the network. The role of cortical injury in disturbing functional network connectivity remains unclear. Future studies can combine resting state functional MRI with diffusion MRI to clarify the role of axonal injury and correlate disease course with the change of network properties. This approach may also be an objective, quantitative imaging tool to monitor effects of therapeutic interventions. It would be also interesting to explore if this approach is useful to detect global and regional reorganization of intrinsic brain networks after early unihemispheric brain injury.

This study has some limitations, and, therefore, the results have to be interpreted cautiously. First, although the excellent reproducibility of the results in one child is encouraging, this will have to be tested in more patients in the future to establish both the short-term and long-term variability of the studied rs-fMRI variables, before a clinical use of this approach could be contemplated. Second, one may be concerned that the assumption of coupling between the blood oxygen level dependent signal and neuronal activity may be violated due to impaired vasoreactivity, which has been described in Sturge-Weber syndrome previously [Namer, 1995; Okudaira, 1997; Aylett 1999; Oguz 2007]. This would make the interpretation of the observed signal changes difficult. However, several previous studies found the decreased hemodynamic response being the most prominent in brain regions *remote* from the primary lesion (Okudaira 1997; Aylett 1999; namer 2005), while in the

current study we found network abnormalities corresponding to the lesion region and/or adjacent areas, which were not directly involved in the vascular pathology but whose abnormality had a functional correlate in some of the children. In addition, most previous studies studied Sturge-Weber syndrome blood flow changes under conditions with major blood flow fluctuations, (e.g., during or after seizures) (Aylett, 1999; Namer 2005; Oguz 2007), while resting state fMRI detects subtle blood flow signal fluctuations. Finally, while activation functional MRI is not commonly used in Sturge-Weber syndrome, there is at least one published case where this technique was successful to delineate eloquent cortex before surgery (Stapleton et al., 1997).

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Figure 1.

Eight resting state brain networks utilized to investigate disrupted connectivity in children with Sturge-Weber syndrome. Colored clusters indicate individual regional nodes belonging to the network.

Figure 2.

Multimodal imaging assessment of resting state brain networks in three children with Sturge-Weber syndrome. Yellow arrows indicate the location of cortical hypometabolism in selected planes of PET (1st row) and structural abnormalities on MRI (second row: occipital leptomeningeal enhancement [10-year old]; posterior dominant right hemispheric atrophy [3-year old]; left medial occipital calcified lesion [1-year old]). The images demonstrate that hypometabolic areas on PET extended beyond MRI abnormalities. Global efficiency (third row) of selected functional networks (temporal in the first patient, parietal in the second patient, and occipital in the third patient) was significantly altered in the affected hemisphere, as compared to the intact side (summation of global efficiency in left hemisphere = 0.90 and summation of global efficiency in right hemisphere = 0.55 for left panel, summation of global efficiency in left hemisphere = 0.85 and summation of global efficiency in right hemisphere = 0.69 for middle panel, summation of global efficiency in

left hemisphere = 0.71 and summation of global efficiency in right hemisphere = 0.95 for right panel).

Figure 3.

Comparison of global efficiency, evaluated from three different functional networks, whole hemisphere (left), default mode (middle), and visual (right). The hemisphere network was constructed by combining frontal, parietal, temporal, and occipital networks. Data the 10-year old child, with a moderate right parieto-temporo-occipital lesion (top) was compared with an age-gender matched normal control (bottom), in order to demonstrate the feasibility of the proposed parameter to detect the affected network, which is the right visual network in this specific case. The hemispheric ratio of summation of global efficiency was listed in Table 1.

Figure 4.

High test-retest reproducibility of topologic parameters. Two parameters, global efficiency and local efficiency, were evaluated from two resting state functional MRI data, recorded from the 10-year old child with right parieto-temporo-occipital lesion: first session (left column) and second session (right column). Very high Pearson correlation coefficients were found in individual network parameters between the two sessions: 1.00/1.00 for global efficiency and 0.99/0.99 for local efficiency at left/right hemisphere.

Table 1

MR1 and Glucose PET Findings as Well as Ratios of Global Efficiency Integration, Right/Left, Obtained From Various Functional Networks

Diagnosis	Healthy control	SWS	SWS	SWS
Age (y), gender	9, M	10, M	3, F	1, F
MRI lesion	None	R TPO	R TPO	LO
PET abnormality	–	R TPO	R TPO > F	LO
Rs-functional MRI	right $\approx$ left	right < left	right $\ll$ left	right > left
Hemisphere	1.03	0.64 ^a	0.60 ^a	1.05
Frontal	1.08	0.80 ^a	0.66 ^a	0.96
Temporal	1.03	0.61 ^a	0.31 ^a	1.11
Parietal	1.14	0.92	0.69 ^a	1.05
Occipital	0.93	0.95	0.44 ^a	1.34 ^a
Default mode	1.13	0.92	0.61 ^a	1.04
Language	1.08	0.98	1.09	0.87
Motor	1.01	0.99	1.01	0.93
Visual	0.95	0.77 ^a	0.61 ^a	1.08
Average	1.04	0.84	0.67	1.05
Standard deviation	0.07	0.14	0.25	0.13

Abbreviations: F, frontal; MRI, magnetic resonance imaging, PET, positron emission tomography; R TPO, right temporo-parieto-occipital; LO, left occipital; SWS, Sturge-Weber syndrome

^aDecreased values on the affected side, based on ratios outside the average ratio of all networks $\pm$ 2 standard deviations, measured in a normal control (9-year-old healthy child).